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A Cost-Effectiveness Analysis of Recombinant Human Activated Protein C for Severe Sepsis in the Intensive Care Unit

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Summary of "A Cost-Effective Analysis of Recombinant Human Activated Protein C for Severe Sepsis in the Intensive Care Unit"

By B.J. Manns, H. Lee, C.J. Doig, D. Johnson, and C. Donaldson

Purpose

The purpose of this study is to provide information for decision-makers about the best use of recombinant human activated protein C (APC) in the treatment of severe sepsis in the intensive care unit.

Background

Patients with severe sepsis constitute 6 to 15 percent of admissions to an intensive care unit and have a 30 to 50 percent hospital mortality rate. In Canada, based on an estimated three cases of sepsis per 1,000 population, there were about 93,000 cases of sepsis in 2001. If all septic patients in 2001 had been treated with APC, an additional $1.0 billion would have been required within the Canadian health care system. Considering the estimated cost of APC and the fact that resources will be taken from hospital budget (or health care more broadly) to fund APC, how can the use of this medication be best rationalized?

Approach

Using administrative data, complete clinical and costing information was collected on 787 patients who were admitted with severe sepsis to a Calgary Health Region intensive care unit (ICU) between April 1, 1996 and March 31, 1999. Survivors were followed up to three years after hospital discharge. The clinical and costing information derived from this group was combined with published estimates of the effectiveness of APC to enable an economic evaluation comparing APC with conventional care for the treatment of patients with severe sepsis in the ICU.

Key findings

The authors report the following key findings:

- Treatment of 100 unselected patients with severe sepsis using APC would be expected to save about 6 lives. Based on this study, survivors of sepsis have an average life expectancy of 8.1 years. On the cost side, there is an immediate expense of $1,067,600 ($10,676 X 100 patients for APC), and the cost of caring for six survivors over 8.1 years is $703,784. Using this simple calculation, the cost per life year gained is $36,448.

- If the life expectancy of a sepsis survivor is only two years (due to the presence of other significant comorbid disease), then the cost per life year gained rises to $147,615 per life year gained.

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and

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- A posthoc United States Food and Drug Administration analysis of the study suggested that the clinical benefit of APC was restricted to patients with the greatest severity of sepsis. As such, the cost-effectiveness of APC for patients with less severe sepsis was "very unattractive".
- The pharmacy budget for the Calgary intensive care units was $2.4 million in 2001. During that year, 285 patients were admitted with sepsis syndrome. If all eligible patients with sepsis syndrome were treated with APC, the estimated pharmacy cost in 2001 for APC alone would have been $2.1 million. If only selected patients with severe sepsis received APC, then the estimated pharmacy cost would have been $728,000.

Conclusions

Activated protein C (APC) is a new therapy for patients with severe sepsis who have a high mortality and where alternative therapies do not exist. Using simplified calculations in addition to the more sophisticated analyses performed in this study, it is more appropriate to use APC in patients who would have a longer life expectancy if they survive their episode of sepsis (i.e. those patients without other diseases that significantly limit life expectancy) and in patients who are very ill. The use of APC for patients with severe sepsis, high illness acuity, and a reasonable life expectancy if they survive their bout of sepsis is associated with a cost per quality-adjusted life year gained within the range of other accepted medical therapies.

For more information

Copies of the report are available from the
Alberta Centre for Health Services Utilization Research
- by contacting David Johnson by e-mail at cujecjohnson@shaw.ca
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Alberta Centre for Health Services Utilization Research

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EXECUTIVE SUMMARY

The Issue: Recombinant Human Activated Protein C is a new antisepsis therapy that has been shown to significantly reduce mortality from sepsis in the intensive care unit. A posthoc United States Food and Drug Administration reanalysis of data from the single available clinical trial suggested that the mortality reduction was restricted to patients with greater acuity of illness (i.e., APACHE II scores ≥ 25). Given the uncertainty, the high cost of this drug and since the potential number of patients who will be eligible to benefit from this therapy is high, a full understanding of the effectiveness and cost-effectiveness in different patient populations is essential.

Objectives: To determine the cost-effectiveness of activated protein C versus conventional care for patients with severe sepsis in the intensive care unit overall and according to age and acuity of illness.

Methods: We performed an economic evaluation from the perspective of the health care purchaser evaluating the treatment of patients with severe sepsis in the intensive care unit with activated protein C or conventional care. Data on the cost and clinical effects of conventional care was collected from a population-based patient cohort in the Calgary Health Region; the relative risk of death associated with activated protein C was taken from the current literature. Sensitivity analysis and scenario analyses were performed to check the robustness of the results and aid the decision-making process in different settings and patient groups. Societal cost-effectiveness analysis and cost-utility analysis were also employed to measure the cost-effectiveness of activated protein C from different perspectives.

Results: The incremental cost per life year gained by treating all patients with severe sepsis with activated protein C was CAN $40,550. Due to a higher absolute clinical benefit, it was more cost-effective to treat patients with APACHE II scores ≥ 25 ($35,762 per life year gained) compared to those with lower APACHE II scores ($51,809 per life year gained). For patients with APACHE II scores ≥ 25, the cost per life gained increased with age ($23,817 for patients under age forty; $41,549 for patients ≥ 80). The cost per quality adjusted life year gained by treating all patients with activated protein C, and for those with APACHE II scores ≥ 25 and ≤ 24 was CAN $67,583, $59,603 and $86,348, respectively. When the Food and Drug Administration estimates of effectiveness were considered, the cost per life year gained by treating patients with APACHE II scores ≤ 24 increased to $845,077.

Conclusions: If one considers only health care resource allocation, then to maximize the efficiency with which activated protein C is used, it should be targeted to patients with severe sepsis, high illness acuity (i.e. APACHE II scores ≥ 25) and a reasonable life expectancy if they survive their episode of sepsis. The use of activated protein C is associated with an incremental cost, and resources may need to be taken from within intensive care unit budgets (or health care more broadly) to fund it.

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1.0 INTRODUCTION

Recombinant human activated protein C has recently been shown to reduce mortality from sepsis in hospital intensive care units. [1] There is currently no published study on the cost-effectiveness of activated protein C for the treatment of severe sepsis in the intensive care unit. It is important to subject activated protein C to an economic evaluation in order to aid future decisions as to whether, and to what extent, it should be funded, because of its expense (CAN $10,676 per course of treatment). The objective of this report is to provide evidence to decision-makers about the costs and benefits of activated protein C in a real clinical setting.

1.1 Clinical Background:

Sepsis is defined as "a systemic inflammatory syndrome in response to infection which, when associated with acute organ dysfunction... is said to be severe". [2] It is common, occurring in twenty-five percent of patients admitted to intensive care units and is associated with a high mortality rate, ranging from thirty to fifty percent. [3,4] In the United States, it has been estimated that 750,000 cases occur each year, with a hospital mortality rate of 28.6 percent, which represents 215,000 deaths nationally. [3] As the population ages, it is predicted that the number of cases in the United States will increase 1.5 percent per annum, yielding 934,000 and 1,110,000 cases by the years 2010 and 2020, respectively. [3]

The care of patients with sepsis in the intensive care unit is important but expensive. The direct cost of caring for patients with sepsis has been shown to be six times higher than patients without sepsis [5], with an average total cost of US $22,100 per case. [3]

Recombinant human activated protein C has been found to reduce the mortality rate from sepsis significantly in a randomized trial (the Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis *(PROWESS)* study). [1] The mortality rate was 30.8 percent in the placebo group and 24.7 percent in the activated protein C group, after a study period of twenty-eight days. This represents a 19.4 percent reduction in the relative risk of death and a 6.1 percent absolute reduction, and indicates that an additional life could be saved for every sixteen patients treated with activated protein C. A posthoc United States Food and Drug Administration reanalysis of data from this study suggested that the mortality reduction was restricted to patients with APACHE II scores ≥ 25. It was a relatively safe treatment; serious bleeding was the most common adverse event associated with the administration of the drug, occurring in 3.5 percent of patients treated with activated protein C, compared with 2.0 percent of patients receiving placebo. [1]

We collected complete clinical and costing information on a large cohort of intensive care unit patients with severe sepsis who were managed by conventional care, following all hospital survivors for up to three years after hospital discharge. Using this complete

dataset, and modelling the short-term improvement in survival that would be predicted by use of activated protein C, [1] we evaluated the cost-effectiveness of activated protein C treatment for patients with severe sepsis in the intensive care unit.

2.0 OBJECTIVES

2.1 Primary Objective:

To determine the cost-effectiveness of activated protein C versus conventional care for patients with severe sepsis in the intensive care unit overall.

2.2 Secondary Objective:

To determine the cost-effectiveness of activated protein C versus conventional care for patients with severe sepsis in the intensive care unit, according to age and acuity of illness.

3.0 METHODS

We analyzed the cost per life year gained for activated protein C compared with conventional care for patients with severe sepsis in the intensive care unit who were eligible to receive this treatment. Baseline analyses take the perspective of the health care purchaser; in sensitivity analysis, we consider a broader "societal" perspective incorporating the effect of costs outside the health care system – namely, the indirect costs (in lost production) due to premature mortality. Although guidelines suggest that economic evaluations should attempt to use effectiveness rather than efficacy data, [6] in this situation, only efficacy data from a single trial is available. Within sensitivity analysis, we estimate the impact that a reduction in effectiveness would have on the results. In baseline analyses, no adjustment was made for quality of life in order to estimate quality adjusted life years, due to the lack of valid "utility" weights for survivors of sepsis. Clearly, quality of life is reduced among intensive care unit and sepsis survivors; [7] as such, an adjustment for quality of life is considered in sensitivity analysis.

The outcomes of our analyses were defined as: life years, costs and the incremental cost per life year gained. Costs and life years were both discounted at an annual rate of five percent. Costs were calculated on the basis of 2001 Canadian dollars. All analyses were performed using DATA Pro (TreeAge Software, Inc., Massachusetts). The horizon of the study was extended to a stage where only five percent of the cohort was alive after hospital discharge to capture the major clinical and economic outcomes related to the treatment under study [8]. The same time horizon has been applied to both costs and outcomes.

3.1 Conventional Care Cohort:

To perform this economic analysis, an accurate estimate of the long-term clinical outcomes and associated cost of care for patients surviving an episode of severe sepsis was required. While it is known that mortality rates per year for "sepsis survivors" are higher than for controls with non-infectious diagnoses, [9] the subsequent risk of death per year overall and based on age has not been reported in the literature. As such, we first undertook a large cohort study to determine accurate estimates of subsequent mortality and direct health care costs for patients with severe sepsis who survived to hospital discharge. The local institutional review board approved this study.

The Calgary Health Region services a population of 1.3 million and has three tertiary care hospitals with intensive care units. All patients admitted to these intensive care units have demographic and physiologic data abstracted daily and prospectively to a longitudinal research database. Patients who were admitted to these intensive care units between April 1, 1996 and March 31, 1999 with suspected or known infection were identified. Using this strategy, 819 patients were identified, of whom 787 (96.1 percent) were from Alberta and had a valid health care number enabling accurate patient follow-up. To confirm that our search strategy was identifying patients with severe sepsis, a sample of forty patients was selected randomly, and manual review of the charts was conducted by one of the authors (CJD). Using a priori established criteria consistent with the PROWESS inclusion criteria, [1] the charts were reviewed to determine if the patients met criteria for severe sepsis. Only one patient, who had a perforated bowel, did not meet criteria for severe sepsis (and thus would not have been a candidate for the PROWESS study based on inclusion criteria). Of the remaining thirty-nine patients, twenty-four had refractory shock requiring vasopressor support, and thirty-six of thirty-nine required mechanical ventilation.

The Calgary Health Region Intensive Care Unit database was used to identify and provide baseline information on the 787 patients from our cohort. Linkage with Calgary Health Region Corporate data enabled determination of length of stay and costs in intensive care unit and in hospital, as well as vital status at hospital discharge. Subsequent use of health care resources such as hospital or emergency room visits and physician claims was determined from Calgary Health Region corporate data and Alberta Health and Wellness, respectively. For hospital survivors, subsequent vital status was acquired through a link with the Alberta Vital Statistics registry. To inform the baseline decision analysis, we used the relative risk of death for patients treated with activated protein C from the PROWESS study. Baseline characteristics of the patients are summarized in Appendix A.

3.2 Costs:

To determine the health care costs for patients with severe sepsis treated with conventional care, we estimated the following direct costs for the patients in our cohort: the cost of care per week in the intensive care unit, the cost of care per week on the hospital ward, and the cost of subsequent health care for hospital survivors. All costs

were evaluated in 2001 Canadian dollars. Estimation of indirect costs for survivors of sepsis was problematic since published estimates are not available and we did not have data from our study cohort on employment rates or patient-related time costs after hospital discharge. However, only 16.9 percent of patients under the age of sixty-one who were discharged from a general intensive care unit were subsequently employed.[10] To estimate indirect costs, we applied this estimate of employment rate (16.9 percent for patients under sixty and zero percent for patients greater or equal to sixty) to the average annual gross salary of a full-time Canadian worker (CAN $33,384).[11]

For this conventional care group, the average cost of care per day in the intensive care unit and in the hospital for patients admitted to the intensive care unit with sepsis was determined. From the 787 patients in the cohort, costs were available for 672 patients (demographics, clinical and all other information was available for all 787 patients). Costs were not identified for 115 patients due to unmatched hospitalization visit or unrecorded patient-specific costs. In addition, 213 patients had no patient-specific recorded cost from the Calgary Health Region database; 209 of them had initial visits at the Peter Lougheed Hospital, and the remaining four had visits at the Foothills Hospital. For patients cared for at the Peter Lougheed Hospital, costs were estimated by Calgary Health Region as follows: a list of total costs and total length of stay for patient groups with disease codes pre-defined by Calgary Health Region was obtained, from which the average cost and average length of stay for each disease group was determined. The estimation was based on a weighted-average of all the patients in the Calgary Health Region database, which mainly consisted of patients from the Foothills Hospital. Using this method, a cost estimate for these 213 patients was determined. However, because most of the patients in the study shared the same disease code, the average cost per intensive care unit day was nearly identical regardless of whether the cost estimates from the Peter Lougheed Hospital were included. Moreover, the patients' costs from the Peter Lougheed Hospital lacked variability among patients with different disease severity. Therefore, in this study, we employed only the actual recorded patient-specific costs to enable estimation of a statistical distribution around intensive care unit costs.

Two methods were then used to calculate average cost per day for the 444 patients with patient-specific costs. First, the total intensive care unit cost was divided by the total length of stay and multiplied by seven to acquire the weekly intensive care unit cost. This value was used for the baseline analysis. Alternatively, the average intensive care unit cost per day was determined individually for each of the 444 patients; these values were summed and divided by the total number of patients generating a mean intensive care unit cost per day. Again, multiplying the average intensive care unit cost per day by seven produced the average weekly intensive care unit cost. Sensitivity analysis was performed on this value to assess the effect of different intensive care unit cost estimates on the results of our analysis. The resulting costs from the two methods are summarized in Appendix D.

For hospital survivors, the direct cost of care for the years subsequent to hospital discharge was determined. This data is crucial for forecasting the cost of caring for patients surviving a bout of sepsis. Of the 787 patients, 504 were discharged alive from

the hospital. The cost of care for the three years after discharge was determined, including hospitalization, emergency room and day surgery within the Calgary Health Region, all hospital admissions occurring outside the Calgary Health Region and all physicians' claims. For patients who died, data was censored on the day of death. For patients who had been discharged after March 31, 1999 (n=3), data was censored for the second year and for patients who had been discharged after March 31, 1998 (n=142), data was censored for the third year. This is because cost data was only available up to March 31, 2001. As such, we were able to assess cost for all patients in year one, 440 patients in year two (61 had died in year one), and 275 patients for year three (84 had died in years one and two) in the follow-up cohort. The subsequent average cost of care for the overall group, different age groups and disease severity groups are listed in Appendix E.

3.3 Clinical Effects:

To calculate the cost-effectiveness of activated protein C treatment, we used a Markov model [12]. Given the acuity of illness, we considered weekly transitions between four clinical states: alive in the intensive care unit, alive on the hospital ward, alive at home, and dead. The starting point of the model was based on our cohort of patients with severe sepsis. During each week, members of the cohort ran the risk of death, and transition from the intensive care unit to the hospital ward and subsequently home. The probabilities of transition from one of these predefined states to another in the model for the conventional care strategy were based on the observed hazard rates within our 787 patient cohort (Appendices F and G). In-hospital mortality was confirmed by Alberta Government Services (Vital Statistics). For hospital survivors, the subsequent hazard rate of death was determined using data from Vital Statistics for years one, two and three after hospital discharge (Appendix H). Because we had vital statistics data only until July 1, 2001, the hazard rate of death in year three was right censored for the ninety-six patients who were discharged home after July 1, 1998 and had not yet died. The subsequent risk of death for the three years after hospital discharge is expressed in annual terms (Appendix H); the annual risk is converted using the risk-rate conversion method described in Appendix H to obtain the subsequent weekly risk of death. [13] To account for increasing annual rates of age-related mortality after the three-year follow-up period, we adjusted the annual mortality rate noted in the third year of follow-up for patients by the age-specific increment in mortality rate noted within the Canadian population. [14]

The above hazard rates were also estimated for these 787 patients based on their age (< 40, 40-59, 60-79 and ≥ 80) and admitting Acute Physiology and Chronic Health Evaluation (APACHE) II score (≤ 24, ≥ 25). [15] As patient numbers were small in the < 40 and ≥ 80 age groups, we repeated the analysis using published in hospital mortality rates for these age groups. [3]

3.4 Clinical Effects of Activated Protein C Cohort:

To estimate the increase in life expectancy attributable to treatment with activated protein C, we reduced the risk of mortality noted for the conventional care cohort during the first four weeks of the analysis by the relative risk of death noted in the PROWESS trial (0.80; 95 % CI 0.69, 0.94). [1] Given the absence of data to the contrary, we did not assume any improvement in survival relative to the conventional care group after twenty-eight days. Consistent with published evidence, we assumed no difference in length of stay for survivors treated with activated protein C compared to those treated with conventional care. [16]

3.5 Cost of Care for Activated Protein C Group:

The acquisition cost of activated protein C is CAN $10,676. For patients treated with activated protein C compared to the placebo group, there was a small excess risk of serious bleeding (1.5 percent). [1] Given the cost associated with managing an episode of clinically important gastrointestinal bleeding (CAN $12,216), [17] the additional expected cost of managing bleeding complications per patient treated with activated protein C is CAN $180. Otherwise, the weekly cost of intensive care unit and ward care as well as the direct and indirect costs of subsequent health care for hospital survivors treated with activated protein C was assumed to be equal to patients treated with conservative care.

3.6 Sensitivity Analysis:

Sensitivity analysis is used to explore whether the results of the study are sensitive to the uncertainty inherent in the estimates used for particular variables, or to the assumptions made. It can be used to identify for which type of patient activated protein C may be most effective or most cost-effective. Sensitivity analysis can also be used to determine which variable leads to most uncertainty in results to guide future research.

To facilitate scenario analysis, we repeated the analysis for six different groups of patients based on age and severity of the illness. These groups are divided into four age groups: under 40, 40 to 59, 60 to 79 and ≥ 80, and 2 APACHE II score groups: ≤ 24 and ≥ 25. APACHE II scores are a general measure of disease severity based on admitting physiologic measurements, age and previous health conditions. APACHE II scores range from zero to seventy-one, the higher the score implying a higher risk of in-hospital death. [15] For each of these six groups, the initial and subsequent mortality rate as well as the cost of care is adjusted based on the characteristics of the patients within each group.

We considered the impact of varying the relative risk of death for patients treated with activated protein C within the ninety-five percent confidence interval reported in the original PROWESS trial. [1] We varied in-hospital and subsequent death rates by twenty-five percent to determine the impact on cost-effectiveness. We also performed a

sensitivity analysis varying the cost of hospital and subsequent health care fifty percent since higher hospital costs would be expected in the United States. [18]

Although the treatment was originally reported to be effective in all subgroups, [1] a posthoc analysis performed by the United States Food and Drug Administration using the actual PROWESS trial data reported that patients with APACHE II scores ≥ 25 had more clinical benefit (relative risk of death 0.71, 95 percent CI 0.59,0.85) than those with APACHE II scores ≤ 24 (relative risk of death 0.99, 95 percent CI 0.75,1.30); [19] these Food and Drug Administration relative risks are considered in sensitivity analysis.

3.7 Monte Carlo Simulation:

The standard way of expressing uncertainty in classical statistics is through use of measures of variance, such as the ninety-five percent confidence interval around a mean for normally distributed variables. As highlighted below, this approach is problematic in economic evaluation and has led to the use of other methods designed to deal with and express analytical uncertainty. [20, 21] For instance, uncertainty that exists in probability estimates, or estimates of clinical effectiveness or cost are usually considered with sensitivity analysis.

Classical univariate sensitivity analysis has been criticized since it only considers the uncertainty present in one (or two) variables at a time, and it may underestimate the uncertainty present within a cost-effectiveness ratio. [20, 21] As a result, some analysts have attempted to construct ninety-five percent confidence intervals around cost-effectiveness ratios. [20] This presents a statistical challenge since incremental costs (the numerator) and incremental life years gained (the denominator) may not be normally distributed and usually do not meet the assumption of independence. [20] In addition, it may be difficult for decision-makers to interpret the results of an economic analysis in the context of ninety-five percent confidence intervals. [20] Some authors have argued against the use of confidence intervals for cost-effectiveness ratios and have recommended the use of Monte Carlo simulation as performed in this analysis. [22, 23]

Monte Carlo simulation enables simultaneous sensitivity analysis of all uncertain variables. It does so by replacing estimates of probabilities, utilities and costs with specific probability distributions, which are based on the reported means and variances of each variable. [22-24] The analysis is then repeated a thousand times, sampling different values from the appropriate distributions for each of the variables. In such a way, a statistical distribution is built up around the incremental cost-effectiveness ratio giving a better reflection of the uncertainty inherent in the analysis.

With Monte Carlo simulation, one can also consider the uncertainty with respect to the maximum cost per quality adjusted life year that decision-makers would consider acceptable (i.e. some decision-makers will choose only to fund therapies associated with cost per quality adjusted life year ratios less than $20,000;[25] others, with larger budgets, may choose to fund therapies with cost per quality adjusted life year ratios up

to $50,000 to $100,000). This is displayed graphically as a cost-effectiveness acceptability curve demonstrating the probability that the use of activated protein C is associated with a cost per quality adjusted life year gained lower than a range of displayed maximum cost-effectiveness ratios.

We performed Monte Carlo simulation for our overall model, and for subgroups according to acuity of illness and estimate of clinical effect (PROWESS or Food and Drug Administration relative risk of death associated with activated protein C) [1, 19] (Appendix M). Statistical distributions were created around all of the variables for which significant measurement uncertainty existed and for which distributions could be estimated.

The following distributions were considered:

- A beta distribution (range zero to one; shape defined by two parameters, the number of deaths and number of survivors over the given time period) was used to describe the following:
  - the risk of death for hospital survivors after discharge
  - the absolute age-related increment in mortality risk

- A normal distribution (shape defined by mean and standard deviation) was used to describe:
  - intensive care unit and hospital costs during the initial admission, since these were normally distributed (range zero to infinity)
  - the utility associated with sepsis survivors (range zero to one hundred)
  - the relative risk of death associated with activated protein C (range zero to one)

- A lognormal distribution (values bounded by 0 and $+\infty$; shape defined by mean and standard deviation of the distribution of the natural log of the random variable) was used to describe health care costs per year after hospital discharge for survivors since these costs were positively skewed.

4.0 FURTHER METHODOLOGICAL ISSUES

Several methodological issues arise during the economic evaluation, such as which discount rate to use, whether to include future costs, etc. The evaluation is performed in accordance with the Canadian Coordinating Office for Health Technology Assessment (CCOHTA) Guidelines for Economic Evaluation of Pharmaceuticals. [8]

4.1 Discount Rate:

The CCOHTA guidelines recommend the base case discount rate as five percent per year. [8] This rate is varied in a sensitivity analysis, with a discount rate of zero percent (no discounting) at minimum and three percent rate for comparability with future studies

as required by the Washington Panel reference case. [8] It also recommends using the same discount rate for both outcomes and costs to avoid paradoxical results. In sensitivity analysis, the British Medical Journal guidelines of using three percent rate for effects and six percent rate for costs is adopted for comparison purposes. [6]

4.2 Future Costs:

Future costs are judged by their relationship to the intervention. Patients with severe sepsis who would have died can survive sepsis via activated protein C, and they will incur extra health care costs subsequent to discharge. Hence, future costs of care arise as a direct consequence of giving the new therapy. For our analyses, the cost of care after hospital discharge is included to reflect the added future costs related to the new treatment. The subsequent cost of care is the highest in the first year after discharge, but levels off during the second and third year. Thus no adjustment is made to the cost of care over time, and future costs are kept constant after year three.

4.3 Indirect Costs:

There are many opinions in economics as to whether indirect costs should be included in economic evaluations. Some economists argue that indirect costs (in terms of productivity loss) should be ignored because other workers in society can fill the jobs vacated by patients admitted to the hospital, assuming unemployment exists in the workforce. [12] Others have suggested that production losses due to illness do influence the scarcity of resources and therefore should be included in the analysis. [26] Since the perspective of the health care purchaser is taken in this study, indirect costs such as the cost of lost productivity are excluded from the baseline analysis. However, for the study to be comparable with other analyses that have a societal point of view, the human capital approach is employed to assess the indirect costs within sensitivity analysis. The human capital approach is a tool used to measure the value of the healthy time produced by a health care program. Since the utilization of a health care program can be viewed as an investment in a person's human capital, the value of the healthy time produced can be quantified in terms of the person's renewed or increased production in the market-place. [12]

Market wage rates from Statistics Canada were used to assess the present value of future earnings. The average weekly wage rate for people aged twenty-five to fifty-four was CAN $642 in 1998. [27] This number is multiplied by fifty-two to get an estimate of the average annual income ($33,384). A study, which examined health and activity after intensive care, showed that only 16.9 percent of the 207 patients under age sixty-one were in employment three months after discharge. [10] This data is used to derive the indirect costs by taking a product of the proportion of the patients returning to work, the proportion of patients in our cohort under sixty, and the average annual income of $33,384. The indirect costs are subtracted from the subsequent cost of care to reflect the value gained from being in a healthy state. However, there are many measurement difficulties with the human capital approach [10], and these are explored further in Section 7.

4.4 Utilities:

Life years saved is used as the output measure in the baseline analysis. However, our analysis was extended into a cost-utility analysis by deriving the quality adjusted life year gained for each alternative. A quality adjusted life year is calculated by multiplying the number of life years added by a program by a standardized weight (ranging from zero to one) that reflects global health-related quality of life during that time. At present, no published information exists on the utility of sepsis survivors. A utility weight of 0.6 was identified from a study that examined the quality of life for intensive care unit survivors of acute respiratory distress syndrome. [28] We used this estimate for our baseline analysis since acute respiratory distress syndrome is similar to sepsis in terms of mortality rate and acuity of illness, [29] and because SF-36 scores from survivors of sepsis and acute respiratory distress syndrome are similar. [30, 31] Since the effect of activated protein C is to reduce mortality rate rather than improve quality of life, it is assumed that utility scores for survivors who received conventional care or activated protein C would be equivalent. It is expected that incorporating quality adjusted life years into the analysis (i.e. to reflect a "cost-utility analysis") will not change the relative ranking of the two treatments. Univariate sensitivity analysis was also done varying the estimate of utility.

5.0 RESULTS – COST-EFFECTIVENESS ANALYSIS FROM A PUBLIC PAYER PERSPECTIVE (BASELINE ANALYSIS)

Appendix I, in Section 9.9, shows the cost-effecitiveness analysis from the baseline decision analysis. The expected cost of the conventional care is CAN $74,000 and the expected cost of the activated protein C treatment is CAN $90,000, resulting an incremental cost of CAN $15,000. The expected life years gained under conventional care is 5.225 life years versus 5.603 life years gained with conventional care plus activated protein C, with an incremental effect of 0.377 life years. By taking a ratio of the incremental cost and the incremental effectiveness, an incremental cost-effectiveness ratio of CAN $40,550 per life year gained is generated.

6.0 RESULTS – SENSITIVITY ANALYSIS

6.1 Results – One-Way Sensitivity Analysis:

With one-way sensitivity analysis, each uncertain component of the evaluation is varied individually, while the others retain their base-case specifications. It is analogous to the idea of comparative static in economics where we change one variable while holding all others constant. A summary of variables, the ranges varied within and the results from the sensitivity analysis are listed in Appendix J.

The analysis was not sensitive to plausible variations in the risk of death or risk of discharge per week from the intensive care unit or the hospital. The analysis is sensitive to plausible changes in the relative risk of death associated with activated protein C when varied within the ninety-five percent confidence interval reported by the PROWESS study. From the PROWESS study, the relative risk of death with activated protein C is estimated to be 0.8, with a ninety-five percent confidence interval from 0.69 to 0.94. Varying the relative risk within these boundaries, the incremental cost-effective ratio varies from CAN $30,085 per life year to CAN $109,193 per life year. This is important because it is often observed that drugs are less effective in routine clinical practice than in clinical trials. If the true relative risk in actual clinical practice is closer to one, then the use of activated protein C will be associated with a much higher cost per life year gained.

All cost variables were also varied in sensitivity analysis to capture the uncertainty relating to variability in sample data and generalizability of results. Of the costing variables, the analysis was most sensitive to variations in the cost of activated protein C. Due to the fact that hospitals may be able to obtain a better discount on drugs when they are buying in bulk, we varied the cost of activated protein C from a value twenty-five percent below list price to twenty-five percent above list price. As summarized from the appendix, the incremental cost-effective ratio varies from CAN $33,478 per life year gained to CAN $47,623 per life year gained.

To reflect increased health care costs expected in other countries (i.e. United States), all cost factors were increased by fifty percent. Despite that, the incremental cost-effective ratio increased only minimally to CAN $46,442 per life year.

Also, we varied all subsequent costs by plus or minus twenty-five percent to determine if it our analysis was sensitive to the assumption we made about constant health care costs over time. The analysis was not sensitive to changes in this variable; the incremental cost-effective ratio only varied between CAN $38,754 per life year and CAN $42,347 per life year.

We also performed sensitivity analysis on the utility weights. As utility score decreases, the effectiveness of activated protein C (number of quality adjusted life years gained) decreases. As such, the incremental cost-effectiveness ratio increases from CAN $40,550 per life year to CAN $81,101 per quality adjusted life year as the quality of life weight is changed from 1.0 to 0.5.

The results of our analysis were not sensitive to changes in the discount rate; the incremental cost-effective ratio decreased from CAN $40,550 per life year to CAN $28,555 per life year if assuming no discounting. The incremental cost-effective ratio remains in this range when applying the Washington Panel discount rate (three percent) and the British Medical Journal discount rate (three percent for effects and six percent for costs).

6.2 Results – Scenario Analysis:

Scenario analysis is a form of sensitivity analysis, which involves varying two or more inputs at the same time. We created six different scenarios by using different risk of death, cost and relative risk of death with activated protein C as explained in Section 5. The six scenarios include four age groups: < 40, 40 to 59, 60-79 and ≥ 80, and two APACHE II score groups: ≤ 24 and ≥ 25. The results from these groups are enclosed in Appendix K, where the incremental cost-effective ratio ranges from CAN $37,922 per life year to CAN $47,820 per life year (excluding the Food and Drug Administration analysis).

In Appendix K, the incremental cost-effective ratio increases as age increased, except for the age group under forty. It is suspected that this difference is related to the lower risk of death in the intensive care unit among this younger group, due to lower illness acuity at baseline. For instance, the baseline risk of death during the first week for this group is ten percent, compared to twenty-eight percent in the oldest group for the first week.

To address this issue, we repeated the analysis assuming equal illness acuity for all four age groups (i.e. instead of using different mortality rates for different age groups, a single set of in-hospital mortality rates derived from the APACHE II score group ≥ 25 is used for all of the age groups). When this is done, the incremental effectiveness improves significantly from 0.30 life years to 0.82 life years for the group under forty. This reduces the incremental cost-effective ratio from CAN $45,595 per life year down to CAN $23,817 per life year. In Appendix J, the incremental cost-effective ratio can be seen to increase linearly as age increases when the same illness acuity is assumed for all age groups.

The risk of death in the intensive care unit for our patient cohort may not have been precise for two of the groups in our analysis (age < 40 and age ≥ 80 groups) since the numbers of patients in each of these groups was small. As such, sensitivity analyses, varying the risk of death in the intensive care unit, were performed to test how sensitive the results were to uncertainty in this variable. An increase of the risk of death in intensive care units from 1.25 times to two times of those in the baseline analysis displays that the incremental cost-effective ratio is more sensitive to this variable for the age group under forty. The incremental cost-effective ratio decreases from CAN $45,595 per life year saved to CAN $30,533 per life year saved for the age group under forty and from CAN $47,820 per life year saved to CAN $40,234 per life year saved for the age group greater or equal to eighty.

For the two APACHE II score groups, it was more effective and cost-effective to use activated protein C for the APACHE II group ≥ 25 (i.e. the more acutely ill group). Although the incremental cost in the APACHE II score ≥ 25 group was greater, the incremental benefit was relatively larger than the extra cost. As such, the incremental

cost-effective ratio was CAN $35,762 per life year for the APACHE II group ≥ 25 and CAN $51,809 per life year for the APACHE II group ≤ 24 (Appendix K).

6.2.1 Cost-Effectiveness of Activated Protein C based on Food and Drug Administration Reanalysis of Data

As noted, the Food and Drug Administration reanalysis of the PROWESS data suggested that activated protein C was more effective in patients with APACHE II scores ≥ 25 and less effective for patients with APACHE II scores ≤ 24. Repeating the analysis using the Food and Drug Administration relative risks, the incremental cost-effective ratio for the APACHE II ≥ 25 and APACHE II ≤ 24 groups change to $28,756 per life year and $845,077 per life year, respectively.

6.3 Results – Alternate Analytical Methods:

As mentioned in the previous section, cost-effectiveness analyses including both direct and indirect costs and a cost-utility analysis were performed. The incremental cost-effective ratios from all three analyses for the overall group, age groups and APACHE II score groups are summarized in Appendix K.

6.3.1 Cost-Effective Analysis From a Societal Perspective

The effect of using the human capital approach acts to reduce the total cost of the new treatment by including the value of healthy time produced by the activated protein C and hence results in a lower incremental cost-effective ratio for patients under sixty. It is assumed that there is no indirect cost savings for patients over sixty because they do not return to work after discharge from hospital. The incremental cost-effective ratio for the overall patients falls from CAN $40,550 per life year to CAN $39,075 per life year when considering the societal perspective. The reduction is more significant in the two younger age groups because more patients return to the work force after hospital discharge. The cost per life year gained decreases from CAN $45,595 per life year to CAN $40,949 per life year for the age group under forty, and from CAN $37,922 per life year to CAN $34,020 per life year for the age group under sixty.

6.3.2 Cost-Utility Analysis From a Public Payer Perspective

Assuming a quality adjusted life year weight of 0.6 for the overall patients, the incremental cost per quality adjusted life year increases from CAN $40,550 per life year to CAN $67,583 per quality adjusted life year. Incorporation of a quality adjusted life year weight does not change the relative ranking of the incremental cost-effective ratios for the different scenarios considered above.

6.4 Results – Probabilistic Sensitivity Analysis:

Probabilistic sensitivity analyses were performed for the overall group and the two APACHE II score groups using the baseline relative risk reported in the PROWESS study by repeatedly sampling the uncertain parameter values from distributions. In Appendix L, the scatter plots show the distribution of the incremental cost per quality adjusted life year ratios generated from one thousand iterations of the simulation. Each point represents the incremental cost per quality adjusted life year of activated protein C relative to the conventional care. The ellipses are the ninety-five percent confidence interval around the incremental cost-effective ratio points. The slopes of the dashed lines from the graphs represent a hypothetical maximum cost per quality adjusted life year that decision-makers would consider acceptable (i.e. in this analysis, $50,000 per quality adjusted life year was set as the ceiling value). Both the overall and APACHE II score ≤ 24 groups have incremental costs per quality adjusted life year more than $50,000 per quality adjusted life year, while for patients with APACHE II scores ≥ 25, some points fall below the hypothetical $50,000 per quality adjusted life year line. This suggests that, based on a prespecified maximum criterion of $50,000 per quality adjusted life year, activated protein C may be reasonable value for money in this group of patients.

Taking the above concept further, different decision-makers will have different maximum cost per quality adjusted life year thresholds in relation to the funding of their program. [25] In a cost-effectiveness acceptability curve, uncertain variables are varied to determine the likelihood of a therapy being cost-effective at different maximum cost per quality adjusted life year thresholds [20]. Before presenting the results of the probabilistic sensitivity analysis, it is appropriate to briefly describe the general structure of the cost-effectiveness acceptability curve. If no uncertainty existed in any of the input variables, then a cost-effectiveness acceptability curve would appear as a straight vertical line passing through the mean cost per quality adjusted life year gained (in the case of the overall model, $67,583). At this point ($67,583) on the curve demonstrated in Appendix M (Figure I), there is a fifty percent probability of activated protein C being cost-effective, which represents the scenario when the estimates of all of the variables are equal to their mean values (i.e. the centre of their statistical distributions). However, there is uncertainty in the variables of our model and this is reflected in the slope of the cost-effectiveness acceptability curve, which tends to flatten out near the bottom and the top as uncertainty in all input variables reaches a maximum.

Appendix M (Figure II) displays cost-effectiveness acceptability curves for the patients with APACHE II scores ≤ 24 and ≥ 25 considering the relative risk of death for activated protein C reported in the PROWESS study. [1] The probability that the use of activated protein C would be considered cost-effective if a decision-maker's maximum cost per quality adjusted life year gained threshold was $75,000 is nine percent and eighty-three percent for patients with APACHE II scores ≤ 24 and ≥ 25, respectively.

Appendix M (Figure III) highlights the impact of the Food and Drug Administration reanalysis on the cost-effectiveness of activated protein C for patients with severe sepsis. [19] The probability that the use of activated protein C would be cost-effective for patients with APACHE II scores ≥ 25 if a decision-maker's maximum cost per quality adjusted life year gained threshold was $50,000 or $75,000 is fifty-two percent and ninety-three percent, respectively. Due to the very small incremental gain in quality adjusted life years predicted by the use of activated protein C for the APACHE II score ≤ 24 group, the curve for this group is very wide. Despite this uncertainty, the probability that the use of activated protein C would be cost-effective at a level less than $1,000,000 per quality adjusted life year gained for patients with APACHE II scores ≤ 24 is very low (less than one percent).

7.0 DISCUSSION

In this section, the implication of the results derived from the earlier sections will be discussed. Although this paper has attempted to provide as much information as possible to enable the decision-making process, there are some issues regarding the methodology and the interpretation of the results that should be explored before a conclusion is reached. These areas include the incremental cost-effective ratio values, interpretation of a simplified model, limits of the human capital approach, as well as issues related to opportunity costs and allocated efficiency.

7.1 Implications:

This study found activated protein C to be more effective and more expensive than conventional care for patients with severe sepsis in the intensive care unit. If activated protein C is used to treat sepsis patients in the intensive care unit, an extra cost of CAN $15,000 per patient will be incurred. Based on the estimation of three cases of sepsis per one thousand population, [3] there were approximately ninety-three thousand cases of sepsis in Canada in 2001 (Statistics Canada shows that the population in 2001 is 31,081,900). If all of these patients had been treated with activated protein C, an extra CAN $1.4 billion would have been required within the health care budget. This is likely an overestimate given that some of these patients would not have had "severe sepsis" or would not have been candidates for activated protein C. However, it does highlight the magnitude of expenditure that would be expended on such a therapy.

Activated protein C is more cost-effective when used in younger age groups. Moreover, it is more cost-effective to use activated protein C in sepsis patients with higher illness acuity (APACHE II score ≥ 25) because more lives can be saved among individuals with a baseline higher risk of death. Thus, the marginal effectiveness for this group of patients is relatively higher although the incremental cost has also increased. Given resource limitations, it may be most efficient to treat patients under the age sixty, who have an APACHE II score ≥ 25.

There are several strengths of our study. Our study design conforms to existing guidelines set out for the performance of an economic evaluation. [8] The effect of uncertainty on the results of this economic evaluation was investigated fully and our analysis was generally robust to the uncertainty in the variables tested. The results obtained from the health care purchaser perspective were consistent with those taken from a broader societal perspective. By modelling the effect of the intervention on a population-based cohort of patients for whom follow-up on mortality and resource use was essentially complete for three years, we feel that the transparency and generalizabililty of our results is enhanced.

7.2 Simplified Economic Model:

Those unfamiliar with decision analysis may find the modelling and statistical techniques to be complex and nontransparent. Below, we present a simple model that approximates the results of our Markov analysis. Treatment of one hundred unselected patients with severe sepsis using activated protein C would be expected to yield an additional six survivors. [1] Our model predicts that survivors of sepsis have an average life expectancy of 8.1 years (total life years gained by activated protein C treatment of one hundred patients = 48.6 years). On the cost side, there is an immediate expense of $1,067,600 ($10,676 X 100 patients), and the cost of caring for six survivors over 8.1 years is $703,784 (based on data reported in Appendices A and E). Using this simple model, the cost per life year gained is $36,448 ($1,771,384 / 48.6 years), similar to that reported in Appendix K. Using our simplified model, it can also be shown that it may be appropriate to target activated protein C to patients who would have a longer life expectancy if they survive their episode of sepsis (i.e. those patients without comorbidities that significantly limit life expectancy). For instance, if the life expectancy of a sepsis survivor is only two years (due to the presence of significant comorbid disease), then the cost per life year gained rises to $147,615 per life year gained ($246,025 per quality adjusted life year gained).

7.3 Human Capital Approach:

There are some limitations of the human capital approach to estimate the indirect costs of the disease. First, there are often imperfections in labor market and wage rates may reflect inequities such as discrimination by race or gender. [12] Payment for work performed is not a legitimate measurement of the real production losses for society. Second, it does not consider the value of healthy time gained that is not sold for a wage. People who are unemployed, retired or homemakers, will have no market value. If health resources are allocated according to this criterion, health care programs directed to working people will be more cost-effective than other programs. The principal of equal access for all populations to health care will be violated because there is discrimination against non-working individuals. [32] It is also argued that real production losses for society are much smaller because sick employees can work harder when returning to work, or they can be simply replaced by other unemployed workers in the long run. [26]

7.4 Interpretation in Light of Opportunity Cost and Allocated Efficiency:

More fundamentally, the results of this study need to be understood within the contexts of the opportunity cost related to a decision to fund activated protein C and the allocated efficiency issues thus raises. In many respects, in a publicly funded health care system in which funds for the intensive care unit are likely to continue to be limited, the idea of willingness to pay thresholds may be less helpful for clinical decision-making. The basic result shown by this study, however, is that to achieve health gains with activated protein C, extra resources are required, and likely in differing amounts for different patient groups. To illustrate the idea of combining cost and effectiveness, a simple framework for decision-making is offered (Appendix N). [33] If a new treatment is less costly but the outcome is the same or better than the conventional care, it is preferred and it is a better use of health care resources. This is the scenario reflected in boxes A1 and A2 of the decision-making matrix in Appendix N. On the other hand, if a health program can improve health outcome without increasing the cost, it is also an efficient use of health care resources as shown in box B1. Correspondingly, there are three boxes that contain crosses where the new treatment would be dominated by the conventional care. However, in the gray areas within the matrix, the new treatment results in a better outcome but at higher costs or a worse outcome at lower costs. Judgment is required to decide whether extra resources should be used for the gains in health, since treating the same number of patients by this option will imply allocating more resources to them and less to others.

Activated protein C fits into cell C1 of the matrix in Appendix N. Thus, whether or not the computed incremental cost-effective ratios fall above or below a willingness to pay threshold, intensive care unit managers and physicians will have to decide from where else in their budget such resources will be found. Increasing funding to the sepsis patients will mean reducing resources available to other patients or other treatments for the same patients. Furthermore, it is likely that intensive care unit managers and physicians will have to prioritize which type of septic patient should receive treatment with activated protein C based on clinical characteristics including age and illness acuity. If one considers only health care resource allocation, then to maximize the efficiency with which activated protein C is used, it should be targeted to patients with severe sepsis, high illness acuity (i.e. APACHE II scores ≥ 25) and a reasonable life expectancy if they survive their episode of sepsis.

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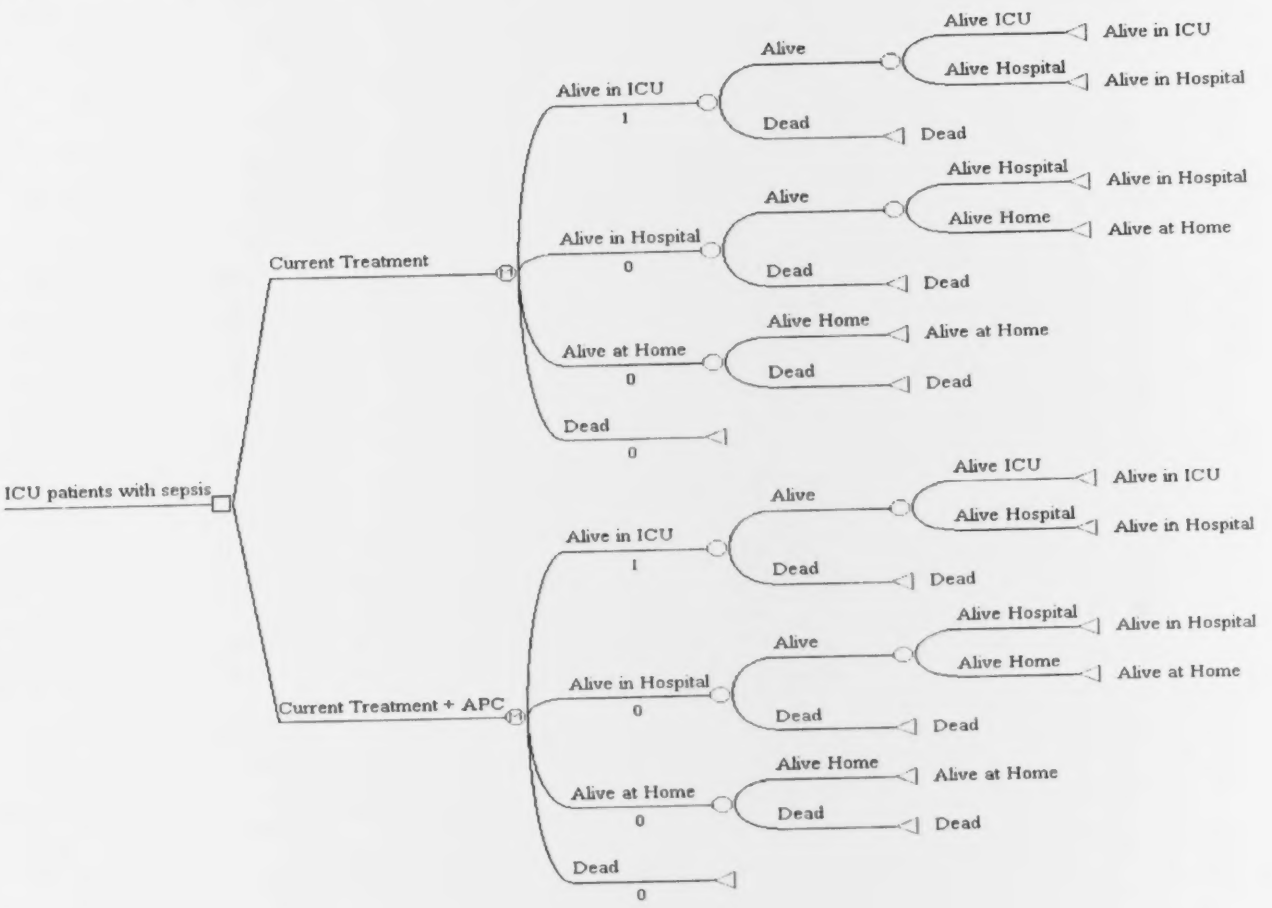
9.0 APPENDICES

9.1 Appendix A: Baseline Patient Characteristics During Their Initial Hospital Stay; Overall, and by age Group and APACHE II Score

	Overall	Age				APACHE II score	
	n=787	< 40 n=89	40-59 n=203	60-79 n=386	≥ 80 n=109	≤ 24 n=519	≥ 25 n=268
Mean APACHE II score (95 % CI)	20.9 (20.3, 21.6)	17.4 (15.2, 19.5)	19.6 (18.3, 21.0)	22.0 (21.1, 22.9)	22.4 [b] (20.8, 24.0)	15.5 (15.1, 16.0)	31.8 (31.2, 32.5)
Male gender (%)	55.8%	50.6%	54.7%	59.1%	50.5%	57.2%	52.0%
Mortality at 28 days (%)	242 (30.7%)	11 (12.4%)	54 (26.6%)	130 (33.7%)	47 (43.1%)	96 (18.5%)	146 (54.5%)
Mortality at hospital discharge (%)	283 (36.0%)	15 (16.9%)	63 (31.0%)	151 (39.1%)	54 (49.5%)	119 (22.9%)	164 (61.2%)
Mean intensive care unit length of stay, days (95% CI)	6.4 (5.8, 7.1)	8.0 (5.5, 10.5)	6.2 (5.1, 7.2)	6.6 (5.7, 7.6)	5.0 (3.6, 6.3)	5.8 (5.1, 6.4)	7.8 [c] (6.4, 9.3)
Mean ward length of stay, days (95% CI)	29.1 (26.6, 31.7)	32.6 (23.9, 41.3)	29.2 (23.8, 34.6)	30.1 (26.5, 33.8)	22.5 (18.0, 26.9)	30.7 (27.7, 33.7)	24.9 [c] (20.5, 29.2)
Mean cost in intensive care unit [d] (95% CI)	$30,188 (27,807, 44,394)	$36,059 (17,985, 53,028)	$31,091 (24,554, 45,722)	$30,790 (25,785, 45,279)	$20,429 (13,757, 30,043)	$26,729 (23,074, 39,308)	$37,032 [c] (28,194, 54,459)
Mean cost in ward [d] (95% CI)	$18,268 (16,157, 26,864)	$19,812 (13,640, 29,135)	$19,535 (14,700, 28,728)	$18,056 (15,021, 26,553)	$15,057 (11,556, 22,143)	$19,551 (16,924, 28,752)	$14,591 [c] (11,662, 21,458)

[a] The intensive care unit admitting diagnoses were unspecified septic shock (41.5%), pneumonia (33.8%), gastrointestinal perforation (12.8%), ischemic bowel (5.8%), intra-abdominal infection without perforation (4.2%), necrotizing fasciitis (1.0%), and meningitis (0.9%).
[b] $p < 0.001$ for comparison of the four age groups using one-way ANOVA
[c] $p < 0.05$ for comparison of the two APACHE II groups using two-sided t-test
[d] includes all hospital costs and physician claims

9.2 Appendix B: Decision Tree Modelling the Impact of Activated Protein C on Patients with Severe Sepsis in the Intensive Care Unit



9.3 Appendix C: Baseline clinical and costing variables

Variable	Value	Reference	Plausible range considered
Cost of activated protein C	$10,676	Eli Lilly and Company	$1,000 - 13,345
Cost of complication from activated protein C	$180	[17]	$90 - 360
Weekly intensive care unit cost	$23,425 [1]	Calgary Health Region database	$15,278 - 23,975
Weekly hospital costs	$4,811 [1]	Calgary Health Region database	$3,398 - 7,301
Subsequent cost of care	Appendix E	Calgary Health Region database	+/- 50%
Relative risk of death on activated protein C	0.800	PROWESS study [1]	0.69 -0.94
Risk of death in intensive care unit and hospital	Appendix F	Alberta Vital Stats / intensive care unit database	+/- 25%
Risk of discharge from intensive care unit	Appendix G	Calgary Health Region database	+/- 25%
Risk of discharge from hospital	Appendix G	Calgary Health Region database	+/- 25%
Subsequent risk of death	Appendix H	Alberta Vital Stats	+/- 25%
Discount rate for costs	0.05	[8]	0.00 - 0.06
Discount rate for effects	0.05	[8]	0.00 - 0.05

[1] See Appendix D for alternate cost calculation.

9.4 Appendix D: Cost of Initial Intensive Care Unit and Hospital Stay

	Default Method: Divide total costs by total length of stay.	**Alternate Method:** Find the cost per day for each patient, and then take an average from the distribution.
Total intensive care unit Costs	$12,073,075	-
Total intensive care unit length of stay (days)	3,877	-
intensive care unit Cost per day (95 % CI)	$3,114	$3,669 ($3,113 - $4,225)
intensive care unit Cost per week	$21,798	$25,682
Total Ward Costs	$7,686,593	-
Total Ward length of stay (days)	11,070	-
Ward Cost per day (95 % CI)	$694	$1,117 ($920 - $1,315)
Ward Cost per week	$4,861	$7,822

9.5 Appendix E: Average Annual Subsequent Cost of Care (per Patient)

	Overall	Age groups				APACHE groups	
Year 1	(n=502)	< 40 (n=74)	40-59 (n=139)	60-79 (n=234)	≥ 80 (n=55)	≤ 24 (n=400)	≥ 25 (n=94)
Calgary Health Region costs							
Hospitalization[1]	$16,534	$14,701	$16,802	$18,097	$11,669	$14,328	$25,849
(Mean, Std Dev)	(33,409)	(29,432)	(29,642)	(38,636)	(21,408)	(25,802)	(54,883)
ER	$276	$205	$294	$318	$150	$286	$225
(Mean, Std Dev)	(450)	(319)	(534)	(466)	(223)	(459)	(406)
Day Surgery	$36	$57	$20	$44	$12	$38	$15
(Mean, Std Dev)	(317)	(223)	(116)	(437)	(86)	(349)	(101)
Subtotal Calgary Health Region costs							
Mean	$16,846	$14,964	$17,116	$18,460	$11,830	$14,653	$26,089
(95 % CI)	(13,908, 19,784)	(8,142, 21,786)	(12,116, 22,115)	(13,474, 23,446)	(6,022, 17,639)	(12,103, 17,202)	(14,839, 37,339)
Median	$3,759	$999	$2,800	$4,548	$4,162	$3,181	$6,885
(25-75% percentile)	(0-19,724)	(0-16,052)	(0-19,724)	(0-24,629)	(0-13,359)	(0-17,089)	(0-29,306)
Mean Physician Billing	$2,115	$2,456	$1,896	$2,315	$1,416	$1,946	$2,818
Mean cost for hospitalization outside of Calgary Health Region	$1,895	$3,021	$1,695	$1,809	$1,284	$2,035	$1,281
Total expenses	**$20,855**	**$20,441**	**$20,707**	**$22,584**	**$14,530**	**$18,634**	**$30,188**

[1] Including nursing, medications, labs, diagnostic imaging, support staff, surgery and supplies.

	Overall	Age groups				APACHE groups	
Year 2	(n=440)	<40 (n=68)	40-59 (n=124)	60-79 (n=203)	≥ 80 (n=45)	≤ 24 (n=355)	≥ 25 (n=77)
Calgary Health Region costs							
Hospitalization[1]	$3,222	$1,861	$4,073	$3,370	$2,262	$3,130	$3,976
(Mean, Std Dev)	(9,953)	(7,385)	(13,925)	(8,298)	(6,418)	(9,272)	(13,041)
ER	$155	$89	$171	$181	$91	$164	$129
(Mean, Std Dev)	(433)	(236)	(525)	(457)	(195)	(447)	(382)
Day Surgery	$21	$20	$19	$27	$0	$25	$5
(Mean, Std Dev)	(138)	(117)	(148)	(153)	(0)	(152)	(44)
Subtotal Calgary Health Region costs							
Mean	$3,398	$1,970	$4,263	$3,579	$2,353	$3,320	$4,110
(95 % CI)	(2,443, 4,352)	(113, 3,827)	(1,751, 6,775)	(2,390, 4,767)	(375, 4,330)	(2,324, 4,315)	(1,115, 7,105)
Median	$0	$0	$0	$0	$0	$0	$0
(25-75% percentile)	(0-566)	(0-52)	(0-2748)	(0-2327)	(0-0)	(0-1171)	(0-312)
Mean Physician Billing	$1,478	$1,983	$1,321	$1,530	$882	$1,489	$1,428
Mean cost for hospitalization outside of Calgary Health Region	$2,033	$2,944	$1,876	$1,912	$1,574	$2,138	$2,874
Total expenses	**$6,909**	**$6,897**	**$7,460**	**$7,021**	**$4,809**	**$6,947**	**$8,412**

[1] Including nursing, medications, labs, diagnostic imaging, support staff, surgery and supplies.

	Overall	Age groups				APACHE groups	
Year 3	(n=275)	<40 (n=41)	40-59 (n=87)	60-79 (n=122)	≥ 80 (n=25)	≤ 24 (n=243)	≥ 25 (n=27)
Calgary Health Region costs							
Hospitalization[1] (Mean, Std Dev)	$3,381 (9,999)	$1,758 (6,257)	$2,791 (6,975)	$4,489 (12,992)	$2,698 (6,193)	$3,413 (10,336)	$2,945 (6,724)
ER (Mean, Std Dev)	$179 (550)	$112 (291)	$160 (327)	$221 (750)	$147 (273)	$156 (350)	$409 (1410)
Day Surgery (Mean, Std Dev)	$11 (82)	$0 (0)	$13 (89)	$16 (98)	$0 (0)	$7 (66)	$24 (122)
Subtotal Calgary Health Region costs							
Mean (95%CI)	$3,572 (2,351, 4,792)	$1,870 (0, 3,914)	$2,964 (1,418, 4,511)	$4,725 (2,338, 7,113)	$2,845 (215, 5,474)	$3,576 (2,241, 4,911)	$3,377 (267, 6488)
Median (25-75% percentile)	$0 (0-380)	$0 (0-47)	$0 (0-380)	$0 (0-974)	$0 (0-650)	$0 (0-204)	$0 (0-635)
Mean Physician Billing	$1,400	$1,607	$1,199	$1,565	$976	$1,406	$1,370
Mean cost for hospitalization outside of Calgary Health Region	$1,762	$2,589	$1,883	$1,417	$1,570	$1,809	$1,430
Total expenses	**$6,734**	**$6,066**	**$6,046**	**$7,707**	**$5,391**	**$6,791**	**$6,177**

[1] Including nursing, medications, labs, diagnostic imaging, support staff, surgery and supplies.

9.6 Appendix F: Risk of Death per Week in the Hospital for the 787 Patient Cohort

	Overall	Age				APACHE II Score	
	n=787	< 40 n=89	40-59 n=203	60-79 n=386	≥ 80 n=109	≤ 24 n=519	≥ 25 n=256
1	0.1881	0.1011	0.1576	0.1917	0.2844	0.0790	0.3945
2	0.0798	0.0125	0.0584	0.0897	0.1538	0.0565	0.1548
3	0.0564	0	0.0656	0.0669	0.0500	0.0436	0.1019
4	0.0557	0.0256	0.0455	0.0753	0.0263	0.0467	0.0857
5	0.0670	0.0741	0.0833	0.0396	0.1379	0.0340	0.1321
6	0.0563	0.0500	0.1026	0.0602	0	0.0593	0.0488
7	0.0550		0.0417	0.0345	0.1250	0.0370	0.1111
8			0	0.0217	0.0500	0.0169	0
9			0.0769	0.0500		0.0196	0.1333
10			0.0500			0.0930	0.0500
11						0.0500	

9.7 Appendix G: Risk of Discharge for the 787 Patient Cohort

Week	Risk of discharge from intensive care unit	Risk of discharge from Hospital
1	0.6917	0
2	0.4757	0.2705
3	0.3182	0.4533
4	0.3103	0.3192
5		0.1883
6		0.3281
7		0.2581
8		0.1644
9		0.1613
10		0.1020

9.8 Appendix H: Subsequent Risk of Death for Survivors of Initial Hospital Admission

	Overall	Age				APACHE II Score	
		< 40	40-59	60-79	≥ 80	≤ 24	≥ 25
	n=504	n=74	n=140	n=235	n=55	n=400	n=104
Subsequent annual mortality risk after hospital discharge							
YEAR 1	0.1215	0.0811	0.1079	0.1282	0.1818	0.1125	0.1700
YEAR 2	0.0522	0.0441	0.0403	0.0735	0.0667	0.0338	0.1154
YEAR 3	0.0422	0.0200	0.0465	0.0484	0.1111	0.0408	0.0625

Risk measures are time dependent variables that are sensitive to duration of observation. It was necessary to convert the annual risk of death from the above table into weekly risk of death in order to be used in the decision tree model.

The relationship between risk and rate can be expressed by the following formula:

$\pi = 1 - e^{-\varphi t}$, where π is the risk measurement, φ is the rate measurement and t is the time.

So to convert risk into rate, we take the inverse of the above equation, the rate of death at 1 year is equal to:

$\varphi t = \ln (1/(1- \pi))$

E.g. overall rate of death at year 1 is:

$\varphi t = \ln (1/(1- .1215)) = .1295$

Since rate does not change with time, we can use it to find the weekly risk of death.

$\pi_{1\,week} = 1 - e^{-\varphi t * 7/365}$

E.g. overall weekly risk of death for the first year is:

$\pi_{1\,week} = 1 - e^{-.1295 * 7/365} = .002481$

9.9 Appendix I: Base Case Cost-Effectiveness Analysis, Overall

Strategy	Cost	Marginal Cost	Effectiveness	Marginal Effectiveness	Incremental Cost-Effective Ratio
Current Rx	$74K		5.225 life years		
Activated Protein C	$90K	$15K	5.603 life years	0.377 life years	$40,550 per life year

9.10 Appendix J: Sensitivity Analysis of the Cost per Life Year Gained With Treatment of Patients with Severe Sepsis Using Activated Protein C (Excluding (Indirect Costs)

Variable Used in Analysis	Incremental Cost per Life Year Gained
Overall group (Baseline analysis)	$40,550
Relative risk of death with activated protein C (varied within 95% CI [1])	
Relative risk 0.69	$30,085
Relative risk 0.94	$109,193
Baseline risk of death in hospital	
Risk reduced by 25%	$47,201
Risk increased by 25%	$36,664
Subsequent risk of death for hospital survivors	
Risk reduced by 25%	$36,383
Risk increased by 25%	$44,810
Cost of activated protein C	
Reduced to 75% of list price	$33,478
Increased to 125% of list price	$47,623
Cost of intensive care unit, hospital and subsequent health care	
Reduced by 25%	$37,605
Increased by 25%	$43,496
Increased by 50%	$46,442
Discount rate for costs and effects	
No discounting	$28,555
Costs 3%, Effects 3%	$35,767
Costs 6%, Effects 3%	$34,612
Cost per quality adjusted life year for overall group	
Utility for hospital survivors 0.5	$81,101
Utility for hospital survivors 0.6	$67,584
Utility for hospital survivors 0.7	$57,929
Utility for hospital survivors 0.8	$50,688
Cost-effectiveness of patients with APACHE II ≥ 25, according to patient age (< 40, 40-59, 60-79, ≥ 80) (relative risk from PROWESS trial [1])	
Assuming subsequent mortality for hospital survivors equivalent to:	
< 40 year old age group	$23,817
40-59 year old age group	$27,591
60-79 year old age group	$31,590
≥ 80 year old age group	$41,549

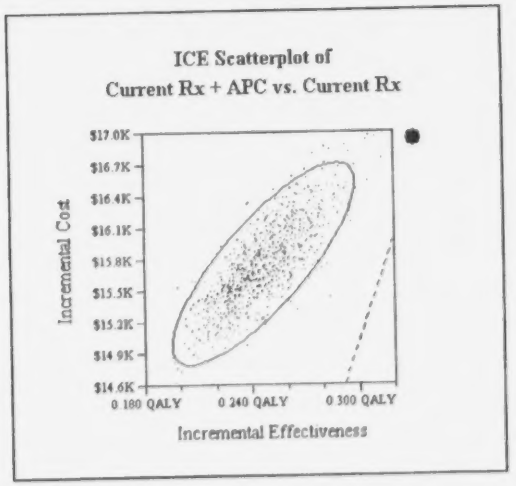
9.11 Appendix K: Scenario Analysis: Overall, by age Group and According to APACHE II Score.

	Overall	Age				APACHE, baseline relative risk From PROWESS		APACHE, relative risk from Food and Drug Administration reanalysis	
		< 40	40-59	60-79	≥ 80	≤ 24	≥ 25	≤ 24	≥ 25
Incremental years of life gained	0.377	0.300	0.397	0.402	0.318	0.264	0.511	0.0130	0.759
Incremental cost per life year gained (Direct costs only)	40,550	45,595	37,922	39,415	47,820	51,809	35,762	845,077	28,756
Incremental cost per life year gained (Direct and indirect costs)	39,075	40,949	34,020	39,415[1]	47,820[1]	49,796	33,817	843,039	26,872
Incremental cost per quality adjusted life year gained (Direct costs only)	67,583	75,992	63,203	65,692	79,700	86,348	59,603	1,408,462	47,927

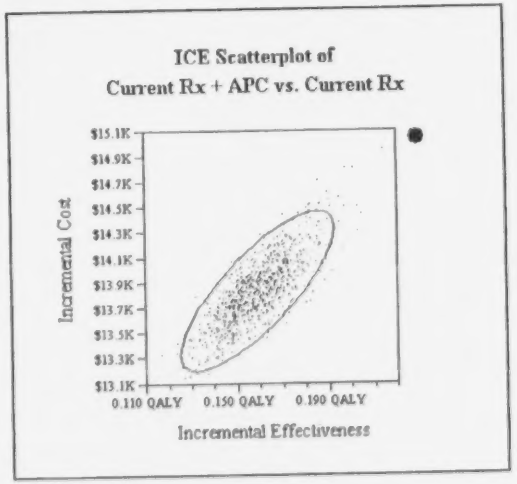
[1] We assumed no indirect cost savings for patients over the age of sixty.

9.12 Appendix L: Incremental Cost-Effective Ratio Scatter Plots

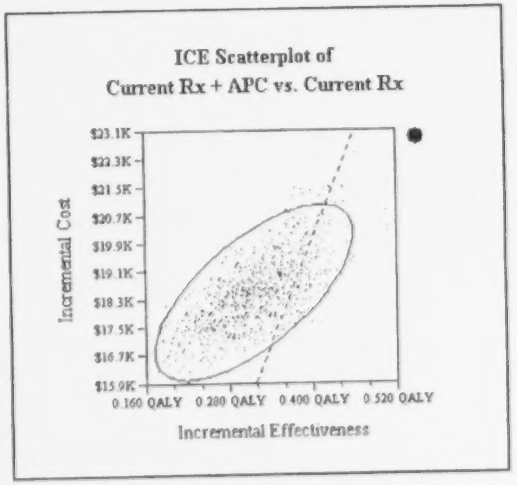
(The ICE scatter plots plot points for all iterations in the simulation. Each point represents the incremental cost and effectiveness of activated protein C relative to the conventional care for a particular iteration. The hypothetical maximum cost per quality adjusted life year ($50,000 in this analysis) is shown as the slope of a dashed line intersecting the origin of the plot. Since the incremental cost per quality adjusted life year is much higher than this $50,000 threshold for patients with APACHE ≤ 24, the line does not appear in this graph. A ninety-five percent confidence ellipse is also shown in all the three graphs.)



Overall



APACHE ≤ 24
Baseline relative risk



APACHE ≥25
Baseline relative risk

9.13 Appendix M: Cost-Effectiveness Acceptability Curves

Figure I: Probability that cost per quality adjusted life year gained from activated protein C is cost-effective (y axis) as a function of a decision-maker's maximum cost per quality adjusted life year gained threshold (x axis) for the overall group.

← $9,114 per quality adjusted life year; treatment of high cholesterol with simvastatin

$105,546 per quality adjusted life year; prophylactic use of defibrillators post-MI ↓

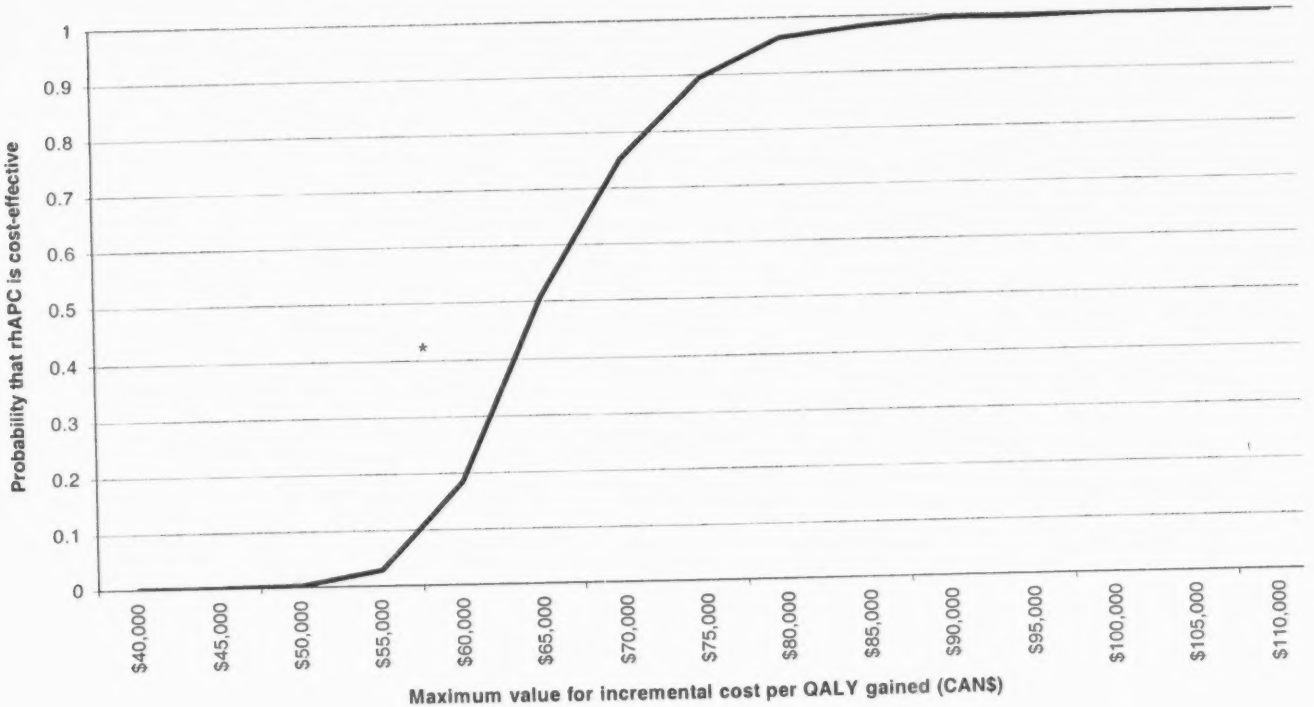


Figure II: Probability that cost per quality adjusted life year gained from activated protein C is cost-effective (y axis) as a function of a decision-maker's maximum cost per quality adjusted life year gained threshold (x axis) for the APACHE score groups using relative risk from the PROWESS study.

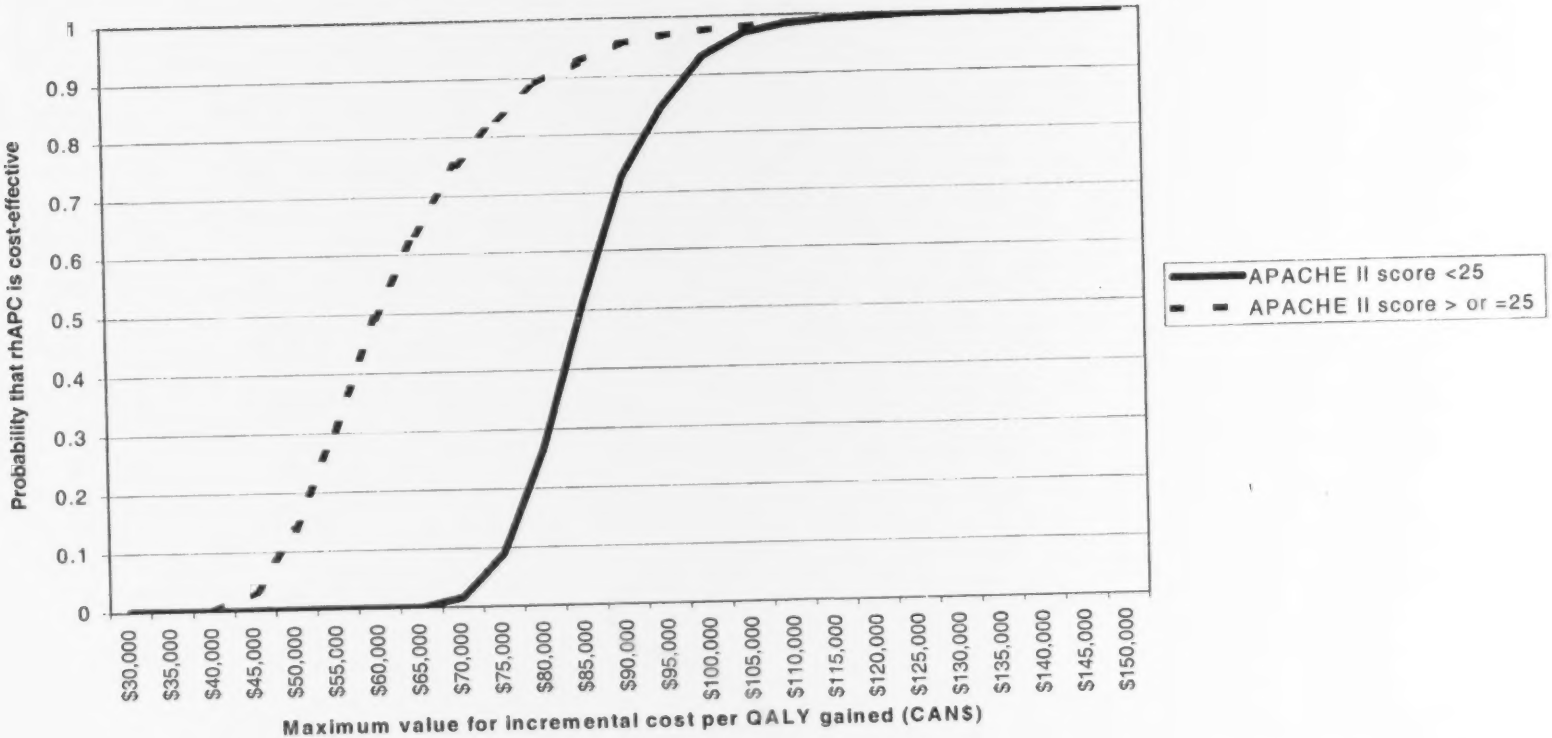
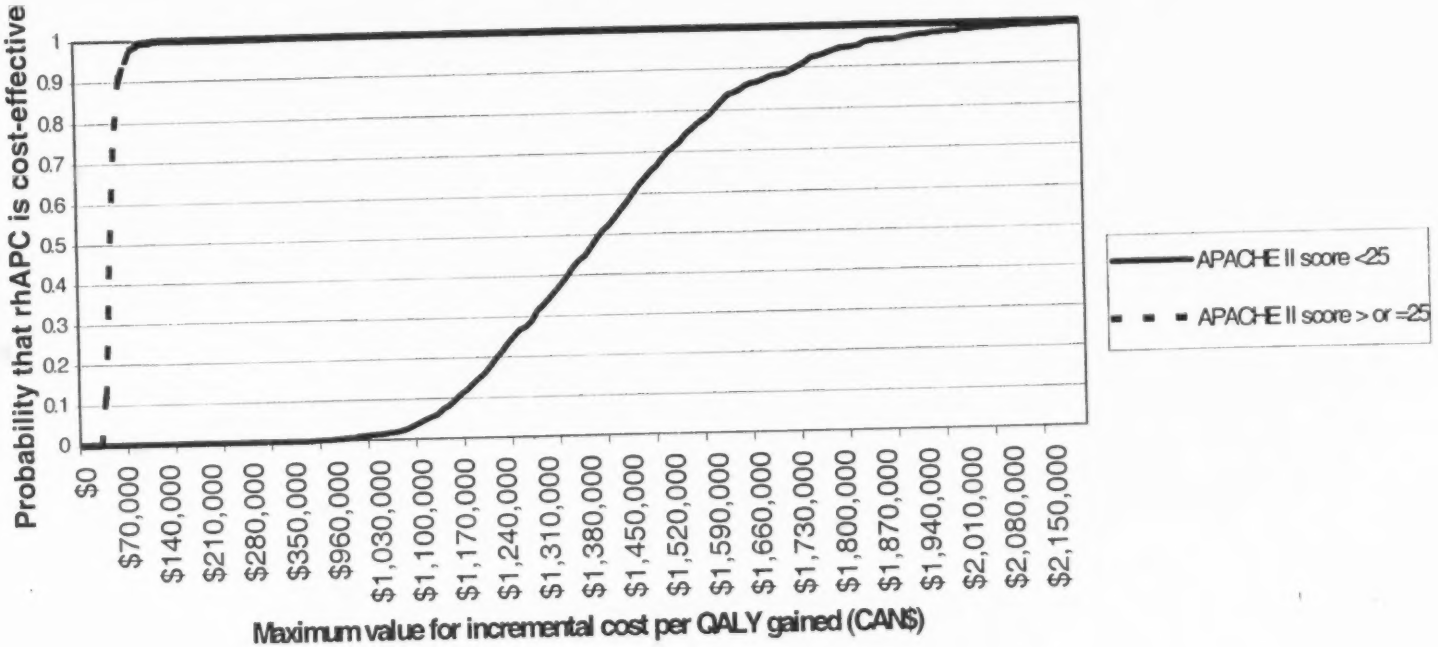
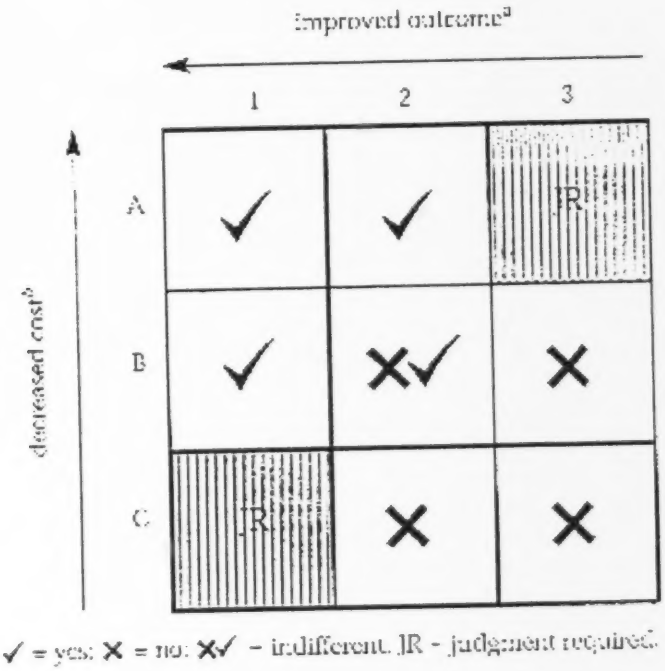


Figure III: Probability that cost per quality adjusted life year gained from activated protein C is cost-effective (y axis) as a function of a decision-maker's maximum cost per quality adjusted life year gained threshold (x axis) for the APACHE score groups using the Food and Drug Administration relative risk.



9.14 Appendix N: Decision-Making Matrix for Cost-Effectiveness Analyses



✓ = yes; ✗ = no; ✗✓ = indifferent; IR = judgment required.

Reproduced from Donaldson, C., Mitton, C., and Currie, G., Managing Medicare: The Prerequisite to Spending or Reform, C.D. Howe Institute Commentary; 157 (January 2002), 1-20.

10.0 BIOGRAPHIES

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Dr. Doig is also the current president of the Alberta Society of Intensive Care Physicians, a member of the national executive of the Canadian Critical Care Society, and was appointed by the Honorable Allan Rock, then Health Minister, to the Canadian Council on Donation and Transplantation, which advises the Council of Deputy Ministers of Health, and the Federal Health Minister on issues pertaining to organ and tissue donation and transplantation.

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